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Balancing between Adaptive and Maladaptive Cellular Stress Responses in Peripheral Neuropathy

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Point mutations in "myelin genes" result in a spectrum of inherited demyelinating neuropathies. The understanding of the pathomechanisms by which these mutations produce phenotypes remains limited. In this issue of *Neuron*, Wrabetz and colleagues report that the unfolded protein response (UPR) is responsible for demyelination in a Charcot-Marie-Tooth disease type 1B (CMT1B) mouse model. Deletion of the UPR mediator transcription factor CHOP completely rescues the motor deficit and ameliorates the neuropathy phenotype.

The molecular cause of demyelinating Charcot-Marie-Tooth (CMT1; [OMIM 118200]) disease in ~70% of patients is a duplication of a 1.4 Mb region on the short arm of chromosome 17 that includes the dosage-sensitive peripheral myelin protein 22 gene (*PMP22*). The reciprocal deletion of the same region is associated with a milder disease, hereditary neuropathy with liability to pressure palsies (HNPP; [OMIM 162500]). Both human studies and animal models reveal that alteration in *PMP22* gene dosage and expression has profound consequences for the development and maintenance of peripheral nerves, suggesting that subtle alteration in synthesis, processing, or degradation can underlie the neuropathy disease process (Lupski and Chance, 2005). Consequently, the regulation of *PMP22* gene expression has been the focus of therapeutic strategies for CMT1A (Sereda et al., 2003; Passage et al., 2004). However, these therapeutic approaches are not feasible for other genetic causes of CMT because such molecular strategies apply only to *PMP22* overexpression.

Mutations in a multitude of different genes, 27 identified thus far, can cause CMT and related peripheral neuropathy disorders. Heterozygous point mutations of several of these genes, such as *PMP22* and Myelin Protein Zero (*P0*), convey dominant traits including Dejerine-Sottas neuropathy (DSN; [OMIM 145900]) and congenital hypomyelinating neuropathy (CHN; [OMIM 605253]), suggesting that the pathomechanism for such mutations may be gain of function, although haploinsufficiency can also cause disease as evidenced by the deletion of *PMP22* causing HNPP (Lupski and Chance, 2005), and nonsense/frameshift alleles in *P0* that cause CMT1B (Inoue et al., 2004). Previous studies have shown that some mutant P0 and PMP22 aggregates colocalize with BiP, an HSP70 chaperone in the lumen of the endoplasmic reticulum (ER) (Matsuyama et al., 2002; Shames et al., 2003). The involvement of mutant proteins with BiP is often hypothesized to result in activation of the unfolded protein response (UPR).

In an exciting study in this issue of *Neuron*, Wrabetz and colleagues extended their previous study in P0S63del mice (a CMT1B model; Wrabetz et al., 2006) and provide direct evidence of UPR activation in S63del transgenic Schwann cells (Pennuto et al., 2008). Deletion of S63 in the extracellular domain of P0 causes CMT1B in humans, and the orthologous mutation in mice results in a similar clinical and neuropathologic phenotype (Wrabetz et al., 2006). Mutant P0S63del is retained in the ER, triggering the UPR as evidenced by significant changes in the UPR markers BiP and CHOP and Downstream of CHOP genes (*DOCs*) (Pennuto et al., 2008). Three key ER-resident transmembrane proteins (IRE-1, PERK, and ATF6), representing different arms of UPR, were shown to be activated. Interestingly, after breeding P0S63del mice to CHOP-deficient ($Chop^{-/-}$) animals, the S63 del-induced motor deficit was rescued, suggesting that CHOP "target genes," as part of a "maladaptive stress response" in Schwann cells, directly cause demyelination. This suppression of the clinical disease phenotype is supported by rescue of delayed F-waves, neuromuscular changes associated with demyelination, and motor capacity in the P0S63del/$Chop^{-/-}$ animals. Beautiful molecular/cellular biological experiments, which alter the hydrophobicity of the P0 β strand C, support the contention that protein misfolding, and not alteration of side chain residues, results in ER retention and UPR activation.

An irony of UPR is that the response leads to the simultaneous activation of both adaptive and proapoptotic pathways. How can the UPR be a primarily adaptive pathway under certain conditions? Ablation of *Chop* partially protects cells from ER-stress-mediated cell death (Zinszner et al., 1998), and the mechanism by which CHOP leads to cell death is not yet known. As a transcription factor, CHOP itself is not intrinsically apoptotic, and it more likely affects the expression of downstream genes, such as *GADD34*, that may facilitate cell death. Thus, it will

be interesting to study additional transcriptional targets of CHOP such as *GADD34* in CMT mouse models. P0-truncating mutants that are associated with the more severe, childhood-onset DSN and CHN have been shown to accumulate primarily within the ER and induce apoptosis (Khajavi et al., 2005). Facilitation of the processing of such mutants from the ER into the cytoplasm is accompanied by a lower number of apoptotic cells (Khajavi et al., 2005). It is intriguing that Wrabetz and colleagues found that the relative amounts of BiP and CHOP differed as a function of the dosage of the S63del expression. They interpreted the increased levels of CHOP in the face of stable BiP that accompanied increased S63del mutant expression as potentially representing a transition from cell survival to an apoptotic response. These latter experiments again clearly stress how important dosage of both normal and mutant myelin proteins can be to dysfunction of the peripheral nerve.

Accumulation of *Pmp22* mutant *Trembler-J* (*Tr-J*) and *Trembler* can also potentially trigger ER stress, resulting in Schwann cell death by apoptosis and, subsequently, causing peripheral neuropathy (Sancho et al., 2001; Khajavi et al., 2007). Although the mechanism through which the processing and function of misfolded or aggregated PMP22Tr-J mutant proteins in cells can be associated with apoptosis has not yet been determined, it is hypothesized that it may include interference with the function of the ER chaperones. Wild-type PMP22 and mutant Tr-J protein form a complex with calnexin, indicating that the sequestration of calnexin might contribute to the disease mechanism by affecting the pathway that controls protein folding (Dickson et al., 2002). In addition, retention of mutant PMP22 in the ER and formation of a complex with calnexin may instead compromise the ability of calnexin to retain GD3 synthase (ST8), a key component for ceramide-induced apoptosis (Tomassini et al., 2004), thus sensitizing the cells to apoptosis. Small molecule compounds that may promote selective and specific alteration of the calcium levels in the ER, or inhibition in any component within the ER stress pathway, have been shown to relieve the toxic effects associated with disease-causing mutations and reverse the potential defect observed in misfolding mutants (Khajavi et al., 2007).

Many diseases are linked to the accumulation of proteins in the ER, suggesting that misfolding often occurs in that compartment. Protein misfolding can contribute to disease through different mechanisms. Disease may result when the efficiency of productive folding/trafficking is reduced to a point at which there is not enough properly trafficked, functional protein to maintain normal physiological function (loss-of-function mechanism). Alternatively, the mechanism could be gain-of-function, in which the aberrant protein actively promotes disease due to changes in normal protein or formation of toxic aggregates such as amyloid (Yang et al., 2004). Additionally, misfolded proteins can accumulate to a level wherein ER-associated degradation (ERAD) gets overwhelmed, resulting in oversaturation of the components of ERAD. For example, the myelin proteolipid protein is produced in vast quantities by myelinating oligodendrocytes. Abnormal amounts of mutant proteolipid proteins in the ER can overwhelm both ERAD and normal export pathways, provoking the UPR and major changes in cell physiology that are closely linked to Pelizaeus-Merzbacher disease (PMD [OMIM 312080]), a CNS dysmyelinating disorder.

It is important to understand the differences in how various myelin gene mutant proteins interact with the protein quality control machinery, because this could provide the basis for determining which chemical chaperone therapeutic strategies might be useful for specific protein folding disorders. Rational drug design could be based on different principles, such as interfering with chaperone activity and allowing misfolded proteins to make their way out of the ER, or involving upregulation at the transcriptional level and modulation of protein folding steps. Wrabetz and colleagues provide us with additional insights into the myriad of potential cellular pathomechanisms underlying inherited peripheral neuropathy.

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